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Increased carotid intima media thickness as an indicator of increased cardiovascular risk in patients with primary familial erythrocytosis

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Abstract

Aim: Erythrocytosis (polycythemia) is defined in males as Hb (hemoglobin) level >16.5 g/dL and Hct (hematocrit) level >49%, while in females, it is defined as Hb level >16.0 g/dL and Hct level >48%. It is classified into two groups based on EPO (erythropoietin) levels: primary and secondary. In the primary group, EPO levels are normal, while in the secondary group, elevated EPO levels are observed. Those carrying JAK2 mutations in the primary group are diagnosed with Polycythemia Vera, whereas those without mutations are defined as familial erythrocytosis. In our study, we aimed to evaluate potential increased cardiovascular risks in patients with primary familial erythrocytosis (PFE).

Material and Methods: A total of 64 patients diagnosed with primary familial erythrocytosis, characterized by normal EPO levels and the absence of JAK2 mutations, were included in the study, along with 30 healthy volunteer controls. The lipid parameters of both groups were examined. Additionally, carotid intima-media thickness (CIMT), considered an indicator of subclinical atherosclerosis in both groups, was measured using non-invasive carotid Doppler ultrasonography (USG).

Results: The lipid parameters of both groups were examined, and no statistically significant differences were detected between the groups. However, in the measurement of carotid intima-media thickness (CIMT), a statistically significant increase was observed in the PFE (primary familial erythrocytosis) group compared to the control group in both carotid arteries.

Discussion: Patients with PFE (Primary Familial Erythrocytosis) being considered as polycythemic but not classified as hematological patients often lead to occasional disruptions in the follow-up and treatment of patients. As demonstrated in our study, PFE patients are prone to increased atherosclerosis and related complications independent of lipid parameters. Considering the hereditary nature of the disease and its onset, particularly in young age, it is important to monitor patients using methods such as Carotid Doppler USG and CIMT, with the belief that this could prevent cardiovascular complications that may occur especially at early ages.

Keywords

Carotid Intima, Cardiovascular Risk, Erythrocytosis, JAK2 Mutations

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Introduction

Erythrocytosis is a group of disorders frequently encountered in haematology practice. Erythrocytosis (polycythemia) is defined as elevated haemoglobin (Hb) and/or haematocrit ratio (Hct) in peripheral blood. This ratio is defined as an Hb value >16.5 g/dL in males and >16.0 g/dL in females and an Hct value >49% in males or >48% in females [1].

Erythrocytosis is basically grouped as primary and secondary according to EPO (Erythropoietin) level, and then both groups are divided into two groups as hereditary and acquired. EPO level is normal in the primary form. Primary Familial Erythrocytosis (PFE) form often involves EPO mutations (germline mutations). Mutations in EPO receptors result in increased erythrocyte production despite physiological EPO levels [2]. This is hereditary and often has a family history of early cardiovascular and cerebrovascular disease events. Primary acquired polycythaemia is Polycythaemia Vera (PV), which involves (somatic mutations; clonal) (JAK2 mutations). Here, JAK mutations are mutations of the JAK2V617F or Exon 12 region. PV is a chronic myeloproliferative disorder involving the bone marrow, with a risk of leukaemia and myelofibrosis [3]. The basic rule in the causes of secondary polycythaemia is elevated EPO. Secondary hereditary type includes germline mutations (VHL, EGLN1, EPAS) and methaemoglobinaemia. Acquired secondary polyschaemia is mainly due to hypoxic causes. In this group of patients, pulmonary, cardiac, endocrine, high altitude and renal transplantation are the main causes.

In the approach to polycythemic patients in haematology polyclinics, if the patient's EPO level is normal, the patient does not have JAK mutations and there are no secondary causes of polycythemia, the patient is considered as PFE, and the patients are followed up with intermittent phlebotomies. Although PFE does not have the risk of haematological malignancy, cardiac and cerebral events at an early age in family members are frequently encountered in the anamnesis of patients. For this purpose, we wanted to evaluate the possible cardiovascular risk in the PFE group and measured carotid intima- media thickness (CIMT) with high-resolution B-mode carotid ultrasonography, which is known to be a suitable method for detecting subclinical atherosclerosis.

Carotid Doppler ultrasonography (USG) is one of the most sensitive and reliable methods for high- resolution morphological evaluation of carotid arteries. Since it is non-invasive, it is one of the most important advantages of the method and the detected CIMT increase is accepted as an early morphological finding of atherosclerosis. In addition to morphological information, colour and spectral Doppler USG has the advantage of showing the flow changes caused by vascular lesions in real time.

The patient's position should be supine, head hyperextended, neck neutral or at a 30-45° angle to the side opposite to the side being evaluated. It is performed using high-resolution, linear aligned probes for examination. The frequency range of the probes is 5-18MHX, and they are designed for vascular purposes.

The examination consists of 3 steps:

1. Real-time B-mode/grey-scale imaging: (axial and longitudinal): It is used for general morphological evaluation. CIMT is used to detect the presence of plaque and to evaluate the plaque structure. CIMT should normally be smaller than 0.8 mm. Exceeding this value is considered to increase the risk of cardiovascular and cerebrovascular events [4].

2. Colour Doppler US (CDUS) (Axial and Longitudinal): A critical level common carotid artery stenosis proximal to the axial axis and the associated external-internal carotid artery steal phenomenon are sensitive in indicating common carotid artery dissection or occlusion, whereas longitudinal axis-CDUS is used to assess whether previously detected plaque-level stenoses cause aliasing.

3. Spectral Doppler US (longitudinal): The most important criterion for determining the presence and severity of carotid artery stenosis is flow velocity assessment [5].

Therefore, we compared Carotid Doppler USG and CIMT of polycythemic patients admitted to the Haematology and Cardiology outpatient clinics of our hospital with a healthy control group in order to evaluate the underlying atherosclerosis and to determine their current cardiovascular risks.

Material and Methods

Patients:

Our study was conducted jointly by the haematology and cardiology clinics of Tekirdağ Namık Kemal University between January 2014 and January 2017. Inclusion criteria included patients with isolated erythrocytosis (haemoglobin [Hb] >18.5g/dL in males or >16.5g/dL in females) and patients with high Hb values. JAK2 V617F and Exon 12 mutation analyses were performed and those who were negative in both tests were included in the study. Serum EPO levels were measured in all patients and patients with normal EPO levels were included in the study. Patients with high EPO levels were excluded. Patients with known severe pulmonary disease (Chronic Obstructive Pulmonary Disease-Bronchial Asthma) and severe cardiovascular disease, known coronary artery disease, atrial fibrillation, atrial flutter, congenital heart disease, history of cardiac operation, congestive heart failure, left bundle branch block were also excluded, and patients under 18 years of age and patients with known cerebrovascular disease or peripheral arterial disease were excluded.

Sixty-four patients evaluated as PFE and 30 healthy individuals constituting the control group were included in the study. After comprehensive clinical evaluations of the patients and the control group, a survey was applied to those who agreed to participate in the study and the patients were questioned in terms of erythrocytosis. In addition, routine laboratory results (blood count and lipid parameters) were recorded. Cardiovascular risk factors (diabetes, smoking, hypertension and lipids) were determined in patients and controls. Written informed consent was obtained from all subjects.

Statistical evaluation:

SPSS for Windows 18.0 software was used to evaluate the statistical analysis. Shapiro-Wilk test was used to examine whether the data were normally distributed. All variables were found to be normally distributed. Continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as number and percentage. In the statistical analysis, continuous variables between the control

and patient groups were compared by Student t test. Chi-square tests were used to compare categorical variables. Pearson correlation analysis was performed to investigate the correlation between values less than .05 and was considered statistically significant in genetic terms.

CIMT measurements:

CIMT measurements were performed after the participants rested for 15 min in the supine position with their heads tilted backwards. The right and left carotid arteries were imaged by an experienced cardiologist using a high-resolution B-mode ultrasound device (GE Vivid S5: General Electric VingMed Systems, Horten, Norway) with a 12L-RS broadband linear transducer. Right and left common carotid arteries were visualised in the longitudinal plane. Measurements were made manually by determining a 1cm segment from 2 cm below the carotid bulb. 3 measurements were averaged. Carotid plaques were not included in the measurement.(Figure:1)

Ethical Approval

This study was approved by the Ethics Committee of Namık Kemal University, Faculty of Medicine (Date: 2015-04-09, No: 2015/48).

Results

A total of 90 people, 64 patients and 30 controls were included in the study. The mean age was 46 years in both groups and there was no age difference between the groups. Again, the gender distribution of males and females was equal and similar to each other. The rates of concomitant hypertension and diabetes were similar in patients and controls in both groups, and there was no difference between the groups. Smoking rates were the same in both groups. Lipid profiles were similar in the form of Triglycerides, HDL-C, LDL-C, Total Cholesterol and there was no statistically significant difference between the two groups for all lipid parameters. The mean Hb level in the patient group was 18.1 g/dL and Hct level was 58.2%, while the mean Hb level in the control group was 14.5 g/dL and Hct level was 43.9%, and there was a statistically significant difference between the groups for both values (Table 1).

CIMT values of the patients were determined as follows. Both CIMT (Right and Left Carotid Intima Media Thickness) were found to be higher in the patient group. Carotid intima-media thickness was significantly increased in the patient groups compared to the control group. A statistically significant difference was found between the groups. This difference was found in both carotid arteries (Table 2)(Figure: 2)

Table 1. Age, gender, and cardiovascular risk factors of the patients and healthy subjects

VARIABLES	PATIENTS (N=64)	CONTROLS (N= 30)	P-value
Age (mean ± SD)	46.33±2.7	46.72±3.1	.879
Gender (F/M), n (%)	3/61 (4.7/95.3)	1/29 (3.3/96.7	.540
Hypertension, n (%)	26 (40.6)	11(36.7	.320
DM, n (%)	6 (9.37	2 (6.66)	.120
Smoking, n (%)	27 (42.2)	27 (42.2)	.680
TC (mg/dL)	193.0±40.3	199.6±47.4	.504
HDL-C (mg/dL	42.1±11.1	41.56±10.2	.825
LDL-C (mg/dL)	118.4±31.4	125.15±40.8	.408
Triglyceride (mg/dL)	176.8±88	176.3±103.8	.981
Hemoglobin (g/dl)	18.1±1.2	14.5±0.8	.001
Hematocrit (%)	58.2±2.7	43.9±1.8	.001

DM = diabetes mellitus, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, SD = standard deviation, TC = total cholesterol. p<0.05 is statistically significant, SD: standard deviation.

Table 2. CIMT thicknesses in patient and control groups

	Patient (n=64)	Control (n=30)	P-value
Right Carotid Intima Media Thickness mm			
(Mean±SD)	0,72±0,17	0,58±0,09	<0.001
Right Carotid Intima Media Thickness mm			
(Med-IQR)	0,7(0,2)	0,6(0,1)	
Left Carotid Intima Media Thickness mm			
(Mean±SD)	0,73±0,17	0,57±0,08	<0.001
Left Carotid Intima Media Thickness mm			
(Mean±SD)	0,7(0,2)	0,58(0,1)	

P value <0.001 is significant. CIMT (Carotis Intima Media Thickness

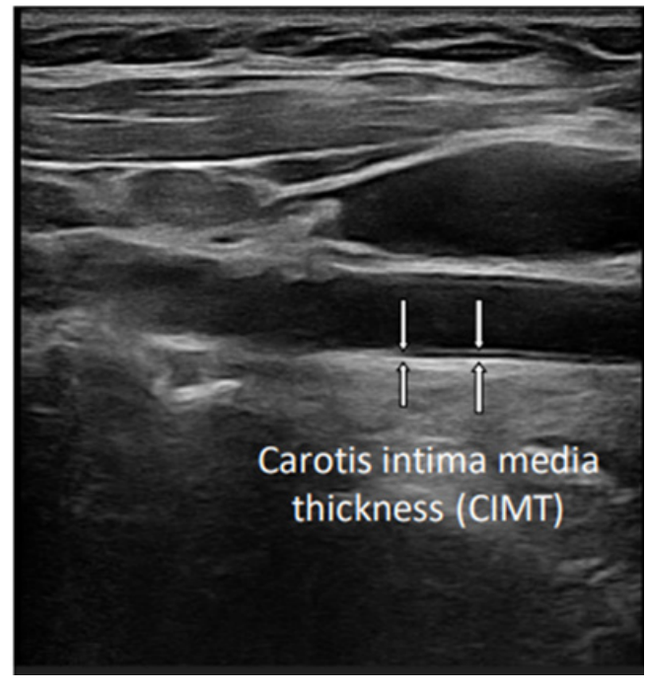

Figure 1. USG image of the IMT

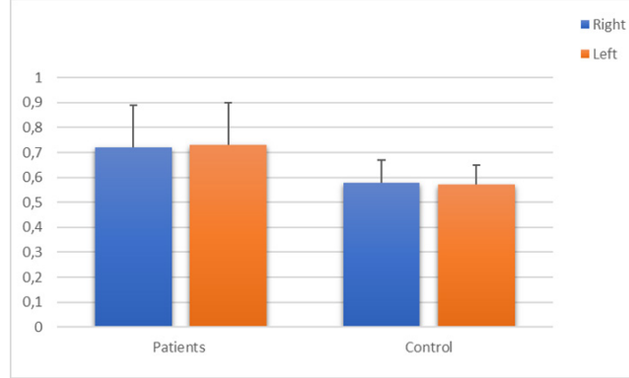

Figure 2. difference in IMT between the control and patient groups

Discussion

Unlike Polycythemia Vera, which is a chronic myeloproliferative disease with polycythemia, PFE does not progress to any haematological disease and does not involve the bone marrow. Therefore, since it is not a disease of the bone marrow and does not cause a secondary haematological disease, it may be ignored in haematology outpatient clinics from time to time. However, in cardiology outpatient clinics, patients tend to be referred to haematology outpatient clinics because of the polycythemic picture present in the patient. As a result, this group of patients may actually be stuck in the middle in terms of follow-up and treatment.

In the analyses we performed in patients presenting with polycythemia in our outpatient clinic follow-up, we observed that this group of patients with negative JAK2 V617F and Exon 12 mutations, no secondary polycythemia and normal EPO values were predominantly male. In retrospective anamnesis, we also observed that sudden death, acute coronary syndrome and cerebrovascular events, which usually occur at young ages, were frequent in this group of patients, especially in first-degree family relatives. Therefore, we planned to investigate this issue to determine the possible increase cardiovascular risk in PFE patients. In our literature review, we observed that the number of studies on PFE is not very high. We did not find any cardiovascular risk studies, especially in this group of patients in our literature review. More frequently, case reports were available.

Since one of the problems that arise in the diagnosis of PFE is the uncertainty and inadequacy in the mutations defining this group of diseases, the diagnosis is based on the exclusion of other secondary polycythaemia and JAK2(+) myeloproliferative diseases. Since PFE-defining mutations are not well characterised, it is not frequently used in clinical practice. These mutations mostly involve amino acid changes in Exon 8 of the EPO receptor gene [6]. However, since the identified mutations cannot be demonstrated in many cases, the term Idiopathic Familial Polycythaemia is also used instead of PFE in some sources [7].

Since cardiac risk studies directly evaluating PFE patients have not been performed, we wanted to evaluate and interpret our study by examining similar studies performed in other groups with polycythemia. Chuvas polycythemia, which is a similar type of polycythemia found in an endemic region in Asia, is an endemic polycythemia with partially similar features to PFE. Chuvas polycythaemia has a proven cardiovascular risk and increased thrombus formation [8]. Premature death and cardiovascular events have been reported in people living in this region, especially in male individuals. An increase in the incidence of cancer was also investigated in this group, but no risk was found [9].

It is accepted that many mechanisms increase cardiovascular events in polycythemia and that this triggers underlying atherosclerosis independently of lipids. One of these views is that moderate hypoxia triggers pulmonary hypertension by increasing ventilation in this group of patients, which may lead to an increased cardiovascular risk. In the same study, increased endothelin-1 levels were found in this group of patients and increased systolic pulmonary pressure was detected by Doppler ECHO in these patients [10]. Endothelin-1 is known to have high vasoconstriction properties in the arterial system. These mechanisms are likely to be present not only in PV but also in all polycythaemias and PFE. In fact, the data of our study support that there is increased atherosclerosis in PFE patients, although there is no difference between lipid parameters in the patient and control groups. Atherosclerosis will lead to thromboembolism and acute coronary and cerebrovascular events

In one of the limited studies conducted on this subject, thromboembolic events observed especially at young ages were associated with PFE [11]. There are case reports linking AEs with EPOR mutation to haemorrhage, DVT, coronary artery disease and MI, though milder in patients with EPOR mutation [12]. It has been shown in some publications and case reports that AE can also lead to abortion in women[13]. Considering all of these, prophylaxis is recommended in all cases of PFE [2]. The possible cause of abortion has been attributed to a thrombus in the placenta.

Haematocrit has the strongest influence on whole blood viscosity. One unit increase in haematocrit can cause up to 4% increase in blood viscosity. As haematocrit increases, blood flow velocity in the vessels slows down considerably due to viscosity due to increased resistance [14]. It is suggested that increased cardiac workload due to increased viscosity as a result of increased erythrocyte mass in polycythemia, increased endothelial shear and endothelial dysfunction contribute to atherosclerosis. Increased viscosity resulting from increased erythrocyte count may lead to hypoperfusion, hypoxia and tendency to coagulation [15]. Another study has also shown that PV is associated with endothelial dysfunction [16]. Myocardial performance index, which indicates systolic and diastolic dysfunction, was found to be impaired for both right and left ventricles in PV. Although studies have not been performed in PFE patients, a similar effect in PFE patients is due to the increased viscosity that occurs rather than the pathogenesis of the disease. In our TÜBİTAK study, we detected diastolic dysfunction in the same group of patients by echocardiography. We attributed this dysfunction to increased cardiac workload due to increased viscosity in PFE patients. In our clinical observations, we observed that cardiovascular events occurred more frequently and severely as Hct ratios increased.

One mechanism that has emerged in recent years involves a study in patients with PV that examined neutrophil-to-lymphocyte ratio (NLR) and carotid plaque burden in patients with essential thrombocythaemia and PV. It was emphasised in the study that a significantly higher rate of carotid plaque was observed in both groups of patients compared to healthy controls [17]. The point to be explained here is to show how a lipid-independent atherosclerosis occurs. Although it is known that elevated white blood cell (WBC) levels are not a direct factor in vascular damage, atherosclerotic plaque development, rupture and thrombosis, the correlation between inflammation and MI was proposed more than 50 years ago. Since then, a great deal of evidence has emerged supporting the important role of inflammation in coronary artery disease (CAD) and other manifestations of atherosclerosis [18].

In this context, it was accepted that immune cells are the

dominant cells in early atherosclerotic lesions and accelerate the progression of lesions with their effector molecules. It was stated that direct activation of inflammation can lead to Acute Coronary Syndrome [19]. Neutrophils are presumed to mediate plaque rupture and thrombosis by secreting proteolytic enzymes that cause vascular damage mediated by the secretion of pro-inflammatory cytokines, activation of coagulation pathways, microvascular occlusion, and myocyte necrosis [20].

Similar mechanisms similar to PV in PFE patients, physiological stress and subsequent activation of the neurohormonal system may lead to cortisol release, mediating increased neutrophil count and relative lymphopenia through apoptosis. Thus, the neutrophil- to-lymphocyte ratio (NLR) may serve as a combined marker for both reactive and adaptive components of the inflammatory response as a result of increased neutrophil counts. All these mechanisms are likely to play a role in the atherosclerosis in PFE patients as in PV.

In our study, we compared current PFE patients with the normal population. Our study was designed prospectively. There was no statistically significant difference between both groups in all lipid sub-parameters in lipid profile examinations. When selecting the control group, the characteristics of the patient group were taken into consideration and care was taken to ensure that they had the same characteristics.

We evaluated the increase in CIMT (carotid intima media) thickness as an indicator of increased cardiovascular risk using high-resolution B-mode ultrasound. CIMT determination with carotid Doppler USG can be used non-invasively as a warning by showing IMT (intima-media thickness) in the early period. Measurement of carotid intima-media thickness by B-mode carotid ultrasonography is a suitable method to detect subclinical atherosclerosis. Carotid intima-media thickness greater than 0.9-1 mm is likely to be indicative of atherosclerosis and increased risk of cardiovascular disease [21]. We found significant and statistical increase in CIMT in the patient group compared to the control group. This increase was interesting because although the lipid profiles were similar in both groups of patients, the carotid intima was thicker in the PFE group. This was evident in the whole group with PFE.

Conclusion

As a conclusion of our study, PFE is a disease that requires joint follow-up in haematology and cardiology outpatient clinics. We believe that it is important for the protection of future generations that family examinations are carried out. We consider that screening of family members is important for preventing future complications and preventive medicine in PFE patients beyond the identification of a possible risk of cardiovascular disease in the patient alone.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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